REMARKS

Claims were 1-38 were pending in the application. Claims 18-35 have been canceled, without prejudice, as being directed to a non-elected invention. Claims 1-17 and 36-38 have also been canceled, without prejudice. New claims 39-70 have been added. Accordingly, claims 39-70 will be currently pending in the instant application upon entry of this Amendment. For the Examiner's convenience, the pending claims are set forth in Appendix A.

Support for the new claims may be found throughout the specification and claims, as originally filed. Support for new claims 43 and 44 can be found in the specification, at least, for example, at page 26, lines 19-34 of the specification. Support for new claims 45- 51, 53-59 can be found in the specification, at least, for example, at page 16, line 14 through page 17, line 24, at page 18, line 33 through page 19, line 21, and at page 3, line 32 through page 4, line 18. Support for new claim 52 can be found in the specification, at least, for example, at page 40, lines 22-34. Support for new claim 69 can be found in the specification, at least, for example, at page 5, lines 1-17. Support for new claim 70 can be found in the specification, at least, for example, at page 26, lines 11-14, and at page 27, lines 9-15. *No new matter has been added.*

Any amendments to and/or cancellation of the claims is not to be construed as an acquiescence to any of the rejections set forth in the instant Office Action, and was done solely to expedite prosecution of the application. Applicants hereby reserve the right to pursue the subject matter of the claims as originally filed in this or a separate application(s).

Sequence Identifiers in Appendices A and B

In paragraph 2 of the instant Office Action, the Examiner states that "[t]his application fails to comply with the requirements of 37 C.F.R. 1.821(d), as the

specification does not provide the appropriate SEQ ID NOS: for nucleic acid and protein sequences. The specification should be amended to insert the appropriate sequence identifying (SEQ ID NO) following each recited sequence (see Appendix A and B)."

Applicants respectfully submit that the sequences listed in Appendices A and B are not critical in determining patentability of the claims. Moreover, Applicants respectfully submit that Appendices A and B contain nucleotide and amino acid sequences which correspond exactly with sequences contained within in the Sequence Listing. Each and every sequence listed in Appendices A and B is annotated by a specific reference number (*e.g.*, RXA00063). These reference numbers are contained within the Sequence Listing itself, and are used to identify each of the corresponding sequences contained in Appendices A and B. Accordingly, Applicants respectfully submit that the instant application complies with the requirements of 37 C.F.R. §1.821(d) and request that the Examiner withdraw the instant objection to the specification. In the event that the Examiner refuses to withdraw the foregoing objection, Applicants submit that upon the indication of allowable subject matter, Applicants will amend the Appendices as suggested by the Examiner.

Rejection of claims 1-17 and 36-38 Under 35 U.S.C. §112, Second Paragraph

In paragraph 4 of the instant Office Action, the Examiner has rejection claims 1-17 and 36-38 under 35 U.S.C. §112, second paragraph, as being indefinite for "failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner is of the opinion that

> claims 1-17 and 36-38 are indefinite because it is not clear as to whether the isolated nucleic acid molecule is a stress, resistance, or tolerance gene, or "portion thereof". Applicants could amend the claims to recite the elected nucleic acid, SEQ ID NO: 1, and specifically what type of gene SEQ ID NO: 1 is. Furthermore, the claims are indefinite because it is not clear as to what is meant by "portion thereof" (i.e. a portion of a stress gene or a portion of a tolerance gene or a combination of a portion of a stress and tolerance gene? It is not clear as to what constitutes a "portion thereof)."

Applicants respectfully traverse the foregoing rejection. However, in the interest of expediting prosecution and in no way conceding the validity of the Examiner's position, Applicants have canceled claims 1-17 and 36-38 and have added new claims which refer to SEQ ID NO:1. New claims 43, 44, 53, 54, 55, 57, 58, and 59 refer specifically to "resistance polypeptides." Moreover, none of the new claims recite the phrase "portion thereof." Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

The Examiner is also of the opinion that "claim 8 is indefinite because it is not clear as to what is meant by "hybridizes...under stringent conditions". Applicants should amend the claims to recite specific hybridization conditions."

Applicants respectfully traverse the foregoing rejection. However, in order to expedite prosecution of the application and in no way acquiescing to the Examiner's rejection, claim 8 has been canceled. New claims 43 and 44 recite specific hybridization conditions. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 1-17 and 36-38 Under 35 U.S.C. §112, First Paragraph, Written Description

In paragraph 6 of the instant Office Action, the Examiner has rejected claims 1-17 and 36-38 under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." In particular, the Examiner is of the opinion that

> The instant specification only describes the isolated nucleic acid from *Corynebacterium glutamicum* consisting of instantly claimed SEQ ID NO:1. The specification further teaches that SEQ ID NO:1 is a gene consisting of 1566 bp. In light of the open claims language used (i.e. a portion of a stress, resistance, or tolerance gene of SEQ ID NO:1, 50% homology to a portion of SEQ ID NO:1, and any fragment of at least 15 contiguous nucleotides of SEQ ID NO:1), these claims encompass

> any full length sequence in which the instantly recited nucleic acids may be embedded, for example the full length genes. Therefore, it has been interpreted that the claims are inclusive of genomic sequences, including intron sequences and regulatory sequences, in addition to the full length cDNA sequence. Furthermore, the claims include language so as to include variants of the disclosed sequences, including intron sequences and regulatory sequences, in addition to the full length cDNA sequence. Furthermore, the claims include language so as to include variants of the disclosed sequences with as little as 50% identity to a portion of the disclosed sequences, and any sequence which hybridizes to the disclosed sequences. Claim 7 is inclusive of sequences from other species, mutated sequence, allelic variance with functional activities distinct from that of SEQ IS NO:1, and a large genus of nucleic acids not described in the specification. However, none of these additional sequences meet the written description provision of 35 USC 112, first paragraph....With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description required more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required.

Applicants have canceled claims 1-17 and 36-38, thus rendering the instant rejection moot as it pertains to these claims. With respect to new claims 39-70, Applicants respectfully traverse the foregoing rejection and submit that there is sufficient written description in Applicants' specification regarding SEQ ID NO:1, nucleic acid molecules with a significant degree of homology to SEQ ID NO:1 and SEQ ID NO:2, as well as resistance polypeptides, to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed as required by section 112, first paragraph (see M.P.E.P. 2163.02). In order to meet the written description requirement of the first paragraph of 35 U.S.C. § 112, it is not necessary that a patent specification describe each and every specific member of a genus recited in a claim.

A claim to a genus of chemical compounds satisfies the written description requirement when its accompanying specification either defines by sequence a representative number of its members falling within the scope of the genus or when its

accompanying specification defines the structural features common to a substantial portion of the genus *(The Regents of the University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)). For reasons discussed in detail below, the instant specification satisfies this requirement for the claimed invention.

The instant specification describes how an allelic variant may be identified or produced and teaches what kind of sequence variation functional and non-functional allelic variants of a polypeptide encoded by SEQ ID NO:1 may have (see, for example, page 27, lines 3-29).

Furthermore, claims 43 and 44 are not directed to any and/or all polypeptides but rather are directed only to those functional resistance polypeptides that are encoded by a nucleic acid molecule with a high degree of identity to SEQ ID NO:1 and which hybridizes to the complement of a nucleic acid molecule consisting of SEQ ID NO:1, in 6X SSC at 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65°C. The recited stringent hybridization conditions determine a specific subgenus of molecules in accordance with the invention, *i.e.*, the subgenus of polypeptides that are functional resistance polypeptides.

Example 14 of the *Revised Interim Written Description Guidelines Training Materials* provides that a claim directed to variants of a polypeptide having SEQ ID NO:3 "that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B" with an accompanying specification that discloses a single species falling within the claimed genus, satisfies the requirements of 35 U.S.C. §112, first paragraph for written description. The rationale behind the foregoing conclusion, as presented by the *Written Description Guidelines*, is that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which Applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity."

Similarly, in the present case, new claims 45 ,46, and 47 are directed to isolated nucleic acid molecules comprising or consisting of a nucleotide sequence that is at least 70%, 80%, or 90% identical to the nucleotide sequence shown in SEQ ID NO:1, wherein

the nucleotide sequence encodes a polypeptide capable of resistance to a chemical stress. New claims 49, 50, and 51 are directed to isolated nucleic acid molecules comprising or consisting of a nucleotide sequence that is at least 70%, 80%, or 90% identical to the nucleotide sequence shown in SEQ ID NO:1, wherein the nucleotide sequence encodes a polypeptide capable of modulating the production of a fine chemical. New claims 53, 54, and 55 are directed to isolated nucleic acid molecules which encode a polypeptide comprising an amino acid sequence at least 70%, 80%, or 90% identical to the amino acid sequence of SEQ ID NO:2, wherein said polypeptide is capable of resistance to a chemical stress. New claims 57, 58, and 59 are directed to isolated nucleic acid molecules which encode a polypeptide comprising an amino acid sequence at least 70%, 80%, or 90% identical to the amino acid sequence of SEQ ID NO:2, wherein said polypeptide is capable of modulating of the production of a fine chemical.

Applicants have disclosed in the instant specification assays for identifying all of the at least 70%, 80%, or 90% identical variants of SEQ ID NO:1 which encode polypeptides capable of modulating resistance to a chemical stress (see, for example, page 16, line 14 through page 15, line 24 and page 54, line 24 through page 55, line 13 of the specification) or capable of modulating production of a fine chemical (see, for example, page 54, line 15, through page 55, line 9 of the specification). Thus, based on the teachings in Applicants' specification, one of skill in the art would conclude that Applicants were in possession of the claimed invention at the time of filing.

With respect to claim 52, which is directed to an isolated nucleic acid molecule which encodes a polypeptide fragment comprising at least 100 contiguous amino acid residues of the amino acid sequence of SEQ ID NO:2, Applicants have described various fragments of the polynucleotides of the invention.

In Example 15 of the *Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, First Paragraph Written Description Requirement* the "theoretical specification" discloses a messenger RNA sequence, SEQ ID NO:1, which encodes a human growth hormone. The "theoretical specification" claims antisense molecules that inhibit the production of human growth hormone. The Guidelines provide that

> [c]onsidering the specification's disclosure of (1) ***the sequence (SEQ ID NO:1) which defines and limits the structure of any effective molecules such that one skilled in the art would be able to immediately envisage members of the genus embraced by the claim*** and 2) the functional characteristics of the claimed invention as well as a routine art-recognized method of screening for antisense molecules which provide further distinguishing characteristics of the claimed invention, along with, 3) the general level of knowledge and skill in the art, one skilled in the art would conclude that applicant was in possession of the invention.....***the claimed invention is adequately described.***

Similar to Example 15 of the *Interim Guidelines*, the instant specification describes the nucleotide sequence of the nucleic acid molecules of the invention (SEQ ID NO:1) ***which define and limit the structure of any nucleotide fragments such that one skilled in the art would be able to immediately envisage members of the genus embraced by the nucleotide fragment claims.***

Moreover, as provided in Example 15 of the *Interim Guidelines*, the generation of oligonucleotide fragments is routine. For example, (as indicated in Example 15 of the *Interim Guidelines*) any specified fragment can be ordered from a commercial synthesizing service. Finally, Applicants' specification teaches how such polynucleotide fragments encoding polypeptides may be tested for activity (see, for example, page 40, lines 22-34 of the specification).

Based on the foregoing teachings in Applicants' specification and the knowledge generally available in the art, one skilled in the art would conclude that Applicants were in possession of the claimed invention at the time of filing of the application. The skilled artisan would also be able to make and use the claimed polypeptide fragments using only routine experimentation.

Accordingly, based on the amendments to the claims and the comments set forth above, Applicants respectfully request reconsideration and withdrawal of the instant rejection under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1-17 and 36-38 Under 35 U.S.C. §112, First Paragraph, Enablement

In paragraph 7 of the instant Office Action, the Examiner has rejected claims 1-17 and 36-38 under 35 U.S.C 112, first paragraph, because, according to the Examiner,

> the specification, while being enabling for an isolated nucleic acid from *Corynebacteriam glutamicum* consisting of instantly claimed SEQ ID NO:1, does not reasonable provide enablement for an isolated nucleic acid from *Corynebacteriam glutamicum* encoding a **portion** of a stress, resistance, or tolerance gene of SEQ ID NO:1, an isolated nucleic acid sequence comprising a nucleic acid sequence that is 50% homologous to a **portion** of SEQ ID NO:1, and an isolated nucleic acid comprising at least 15 contiguous nucleotides of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims....In the instant case, the claims are not commensurate in scope with the enabling disclosure because the claims are inclusive of any nucleic acid that comprises a portion of SEQ ID NO:1, an isolated nucleic acid sequence comprising a nucleic acid sequence that is 50% homologous to a portion of SEQ ID NO:1, and a nucleic acid comprising at least 15 contiguous nucleotides of SEQ ID NO:1. These claims encompass any full length sequence in which the instantly recited nucleic acids may be embedded, for example the full length genes, genomic sequences (i.e. including intron sequences and regulatory sequences), in addition to the full length cDNA sequence, variants of the disclosed sequences with as little as 50% identity to a portion of the disclosed sequence, any sequence which hybridizes to the disclosed sequence, sequence from other species, mutated sequence, allelic variants with functional activities distinct from that of SEQ ID NO:1, and a large genus of nucleic acids not taught in the specification. The specification does not provide any guidance as to how to make and use any of these allelic variants, mutated sequence, etc. that are encompassed by the claims.

Applicants have canceled claims 1-17 and 36-38, thus rendering the instant rejection moot as it pertains to these claims. With respect to new claims 39-70, Applicants respectfully traverse the foregoing rejection.

New claims 39-70 are no longer directed to "a portion" of SEQ ID NO:1 or a nucleic acid sequence that is 50% homologous to a portion of SEQ ID NO:1. Furthermore, as taught in the instant specification, the isolated nucleic acid molecules of

the claimed invention do not include genomic flanking sequence (see page 20, lines 25-36 of the specification).

Furthermore, Applicants' specification discloses ample guidance as to how one of skill in the art would make and use the claimed invention. For example, Applicants discloses how the nucleic acid molecules of the invention may be generated (page 20, line 14 through page 31 line 10 of the specification), and how these nucleic acid molecules may be tested for activity page 16, line 14 through page 15, line 24 and page 54, line 24 through page 55, line 13, and page 54, line 15, through page 55, line 9 of the specification). The instant specification also describes how the isolated nucleic acid molecules of the invention can be used (see, for example, page 45, line 11 through page 46, line 11).

Pending claims 39-56 require that the claimed nucleic acid molecules have a significant degree of identity with the exemplified resistance molecules. The specification provides sufficient guidance teaching the skilled artisan how resistance nucleic acid and amino acid sequences can be selected and/or made. Moreover, the specification teaches that amino acid residues that are conserved among the exemplified resistance proteins, as well as conserved between the resistance proteins of the present invention are not likely to be amenable to alteration (see, for example, page 27, lines 3-15).

Furthermore, Applicants' disclosure provides methods by which a variant resistance polypeptide or a fragment of a resistance polypeptide can be assayed for biological activity, *e.g.*, (see, for example, at least page 54, line 17 through page 55, line 9 of the specification). Applicants' disclosure also provides mutagenesis strategies for resistance proteins which result in increased yields of a desired compound (see page 46, line 19 through page 47, line 9 of the specification).

As the Examiner is aware, it is well known that enablement is not precluded by the necessity for some experimentation (see, *e.g.*, *In re Wands* 8 USPQ2d 1400-1407, 1404 (CAFC, 1988)). Applicants respectfully submit that any experimentation that may be required to select and/or make the claimed nucleic acid molecules, and subsequently practice methods of expressing and producing a polypeptide of the invention constitutes

routine, not undue, experimentation, and therefore the specification clearly enables the pending claims.

Based on the foregoing teachings in Applicants' specification, the skilled artisan would have been able to practice the claimed invention using only routine experimentation. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 1-13, 15-17, and 36-38 Under 35 U.S.C. §102

In paragraph 9 of the instant Office Action, the Examiner has rejected claims 1-13, 15-17, and 36-38 under 35 U.S.C. §102(b) "as being anticipated by Kunst et al (Nature (1997) 390 (6657):249-256) and GenEmbl Accession No. Z99118)." The Examiner is further of the opinion that

> This rejection is based on the elected nucleic acid sequence of SEQ ID NO:1. Kunst teaches a portion of a nucleic acid (i.e. 20 basepairs) that is 100% identical to SEQ ID NO: 1 (see GenEmbl Accession No. Z00118, sequence search result 12). Therefore, this sequence is at least 50% homologous to a portion of SEQ ID NO: 1 (claim 5), and would hybridize to SEQ ID NO: 1 under stringent conditions. With respect to claim 9, the reference teaches the B. subtilis genome, which comprises the nucleic acid of GenEmbl Accession No. Z99118 and many heterologous polypeptides (see abstract and pgs. 255-56). With respect to claims 10-13, 15-17, and 36-38, the reference teaches vectors comprising a portion of the nucleic acid of SEQ ID NO:1, a host cell (i.e. E.coli) transfected with said vectors (pg. 255), and fine chemicals produced by said host cell (pg. 255).
>
> Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Yamane (GenEmbl Accession No. AB000617). Yamanne teaches the nucleic acid which is 52.8% identical to SEQ ID NO:1.

Applicants have cancelled claims 1-13, 15-17, and 36-38, thereby rendering the instant rejection moot as it pertains to these claims. With respect to new claims 43-59 Applicants respectfully traverse the instant rejection for the following reasons.

For a prior art reference to anticipate a claimed invention, the prior art must teach each and every element of the claimed invention. *Lewmar Marine v. Barient* 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987). Kunst, *et al.* disclose a 21 base pair *B. subtilis*

polynucleotide sequence. The nucleotide sequence of SEQ ID NO:1 of the instant invention comprises 1,566 base pairs. None of the new claims are directed to "a portion" of SEQ ID NO:1. A sequence alignment of the ***entire length*** of the nucleotide sequence disclosed by Kunst, *et al.* with the SEQ ID NO:1 would result in a much lower percent identity than the percent similarity noted by the Examiner. Accordingly, Kunst, *et al.* do not teach each and every limitation of claims 43-53.

With respect to new claim 52, Applicants respectfully submit that Kunst, *et al.* do not disclose a nucleotide sequence encoding a polypeptide fragment comprising ***at least 100 contiguous amino acid residues*** of the amino acid sequence of SEQ ID NO:2. Therefore, Kunst, *et al.* do not teach each and every limitation of claim 52. Accordingly, Applicants respectfully request reconsideration and withdrawal of the instant 35 U.S.C. §102(b) rejection.

Yamanne *et al.* do not teach each and every limitation of the new claims. New claims 45-48 are directed to isolated nucleic acid molecules which comprise or consist of a nucleotide sequence which is at least 70%, 80%, or 90% identical to the nucleotide sequence of SEQ ID NO:1. Yamanne *et al.* teaches the nucleic acid which is only 52.8% identical to SEQ ID NO:1. Accordingly, Yamanne *et al.* do not teach each and every limitation of the claim. Based on the reasons set forth above, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection under 35 U.S.C. 102.

Rejection of Claim 14 Under 35 U.S.C. §103

In paragraph 12 of the instant Office Action, the Examiner has rejected claim 14 under 35 U.S.C. §103 "as being unpatentable over Kunst et al. (Nature (1997) 390(6657): 249-256) and GenEmbl Accession No. Z99118), as applied to claim 1-13, 15-17 and 36-38 above, and further in view of Sinskey et al. (USPN 4,649,110)." The Examiner is further of the opinion that

> The teachings of Kunst are presented above. Specifically, Kunst teaches a portion of a nucleic acid (i.e. 20 basepairs) that is 100% identical to SEQ ID NO: 1 (see GenEmbl Accession No. Z99118,

> sequence search result 12). The reference does not teach the host cell that belongs to the genus Corynebacterium. Sinskey et al. teaches the use of Corynebacterium as a host cell for foreign or native genes. In view of the teachings of Sinsky et al., it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used Cornyebacterium as a host cell, instead of E. coli, in order to have had an equally effective host cell for producing a fine chemical.

Applicants respectfully traverse the foregoing rejection. Applicants have cancelled claim 14, thereby rendering the instant rejection moot as it pertains to these claims. With respect to new claim 62, Applicants respectfully traverse the instant rejection for the following reasons.

For the reasons set forth above, Kunst, *et al.* do not teach each and every limitation of the claims from which claim 62 depends, and therefore claim 62 is not obvious in view of Kunst, *et al.* in combination with GenEmbl Accession No. Z99118 and Sinskey, *et al.* (USPN 4,649,110). Accordingly, Applicants request that the Examiner reconsider and withdraw the instant 35 U.S.C. §103 rejection.

CONCLUSION

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

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